AMENDMENTS TO THE SPECIFICATION:

Please substitute the following amended paragraphs [0003], [0011], [0013], [0021], [0022], [0023], [0024], [0064], [0079], [0080], [0082], [0087], and [0125], for the original paragraphs having the same paragraph numbers.

[0003] The invention relates generally to the field of oncology, cancer metastasis and cellular proliferation. In particular, this invention relates to the identification of methods of interrupting certain elements of the cell survival pathway, which then allows for enhanced efficacy of traditional modes of cancer therapy, including chemotherapy and radiation therapy. More particularly, the invention relates to the use of kinase or transcription inhibitors for pre-treatment to sensitize for, or concurrent treatment to potentiate chemotherapy or radiation therapy for treatment of cancers or hyperproliferative disorders. The invention also provides for the use of kinase or transcription inhibitors to downregulate expression of the alpha 5 beta 1 integrins and/or phosphorylation of Akt to treat cancer or hyperproliferative disorders. Blocking antibodies specific for the alpha 5 ~~or~~ beta 1 integrins are also envisioned for use in either pretreatment to sensitize for, or to be used concurrently with chemotherapy or radiation therapy for treatment of cancer or hyperproliferative disorders. Methods of treatment of cancer or hyperproliferative disorders using fibronectin binding blocking peptides to sensitize for or potentiate chemotherapy or radiation therapy are also envisioned by the present invention. Furthermore, the invention relates to methods of use of retinoids to decrease the expression or phosphorylation of Akt and treatment of cancer or hyperproliferative disorders. The instant invention also provides for pharmaceutical compositions comprising, and methods of using the agents of the present invention for treatment of cancer or hyperprolifeartive disorders. Screening methods for identification of novel agents for use in treating cancer or hyperproliferative disorders in accordance with the present invention is also disclosed.

[0011] In a second aspect of the invention, the kinase or transcription inhibitors are used to downregulate expression of the alpha 5 ~~or~~ beta 1 integrins.

[0013] A fourth aspect of the invention provides for the use of antibodies to integrin alpha 5 ~~or~~ beta 1 as pretreatment or concurrent treatment to sensitize for, or potentiate chemotherapy or radiation therapy in the treatment of cancer or hyperproliferative disorders.

[0021] In a yet further preferred embodiment, the kinase or transcription inhibitor downregulates expression of the alpha 5 beta 1 integrins or phosphorylation of Akt to sensitize for or potentiate chemotherapy or radiation therapy in mammals in need thereof.

[0022] An eighth aspect of the invention provides for a method for disrupting survival signaling from the microenvironment in cancer cells, wherein said disrupting results in sensitizing cells to chemotherapy, biological therapies or radiation therapy of cancer micrometastases and hyperproliferative disorders in a mammal. In a preferred embodiment, the integrins ~~are~~ is alpha 5 ~~and/or~~ beta 1 ~~integrins~~ and the extracellular matrix protein is fibronectin. In another preferred embodiment, the cancer is breast cancer or prostate cancer. In yet another preferred embodiment, the method comprises administration of an antibody specific for an integrin or a blocking peptide or modified peptide that disrupts interaction of the integrin with the extracellular matrix. In a yet further preferred embodiment, the method comprising administration of all trans retinoic acid or a retinoic acid derivative. A yet further embodiment comprises decreasing expression of cell surface integrins with a transcription inhibitor, or blocking survival signaling initiated by ligation of integrins by microenvironment proteins. A most preferred embodiment provides for treatment with an inhibitor of a kinase, said kinase selected from the group consisting of MAP kinase, Rho kinase, PI3 kinase and PKC kinase. The most preferred inhibitors are selected from the group consisting of LY294002, UO 126, AG82, Y27632, SB203580, PD169316, PD98059, RO318220, and a 3 transferase inhibitor.

[0023] A ninth aspect of the invention provides for a method for treating hyperproliferative disorders in a mammal, comprising administration of an agent capable

of blocking the binding of integrins with the extracellular matrix. In a preferred embodiment the integrins comprises alpha 5 ~~and/or~~ beta 1 and the matrix is fibronectin.

[0024] A tenth aspect of the invention provides for the use of an agent for the preparation of a composition for treatment of hyperproliferative disorders, said agent capable of downregulation of the expression of the alpha 5 ~~and/or~~ beta 1 integrins and ~~their~~ its binding to the extracellular matrix.

[0064] "Integrins" are intrinsic cell surface proteins. They mediate cell adhesion by binding with components of the extra cellular matrix, such as fibronectin. This adhesion process is closely tied to the cells ability to survive and reproduce. Many different integrins have been discovered and most have similar structural features *eg.* they are heterodimeric transmembrane proteins and contain an alpha subunit and a beta subunit. The major fibronectin receptor on most cells is the alpha 5, beta 1 integrin, also referred to in the present application as $\alpha 5\beta 1$. This integrin interacts with the RGD site of the fibronectin molecule.

[0079] The present invention relates to the novel finding that increased expression of the ~~integrins~~ alpha-5 ~~and~~ beta-1 integrin on metastasized breast cancer cells in the bone marrow transmit a survival signal from matrix proteins in the bone marrow. Ligation of the integrins to fibronectin interrupts integrin-mediated cell death signaling and initiates the cell survival signaling that leads to dormancy, protection from chemotherapy and ultimately relapse in the breast cancer patient. The invention provides for a method to inhibit the expression of ~~these integrins~~ the integrin and to interrupt specific elements of the survival pathway that will allow traditional chemotherapy or radiation therapy to be utilized to kill the remaining cells in the bone marrow and avoid a relapse and ultimately resistance by the cells and the death of the patient suffering from a hyperproliferative disorder such as but not limited to breast cancer, or prostate cancer. The over expression of alpha-5 ~~and~~ beta-1 is down regulated through the use of kinase or transcription inhibitors such as demonstrated in Figure 1.

[0080] The schema of **Figure 1** demonstrates the fate of metastatic cells in the bone marrow and the effect of fibronectin ligation through its integrin receptor alpha 5 beta 1 on maintaining survival and chemoresistance. Disruption of this interaction by decreasing synthesis of ~~these integrins~~ the integrin or disruption of ~~their~~ its interactions with ~~their~~ its ligands would allow the cells to become sensitive to chemotherapy and undergo cell death.

[0082] In particular, the present invention is directed to methods for disrupting survival signaling from the microenvironment in cancer cells, wherein said disrupting results in sensitizing cells to chemotherapy, biological therapies or radiation therapy of cancer micrometastases and hyperproliferative disorders in a mammal. The method comprises blocking the interaction of an integrins with ~~the~~ an extracellular matrix proteins of the microenvironment. ~~The~~ A preferred embodiments includes the alpha 5 ~~and/or~~ beta 1 integrins and the preferred extracellular matrix protein is fibronectin. The invention is directed to treating primary tumors, tumor metastasis, micrometastases and hyperproliferative disorders. A further preferred embodiment is treating breast cancer or prostate cancer.

[0087] To study the molecular basis for the long-term survival of growth arrested cells, a comparison was made between the expression levels of various integrins in breast cancer cells that remained dormant on fibronectin for 3 and 5 days in the presence of FGF-2, to that of actively growing cells on fibronectin. Microarray analysis showed increased expression levels of ~~integrin alpha 5~~ the alpha 5 beta 1 integrin, a fibronectin receptor. Western blots demonstrated that FGF-2 induced an increased expression of both ~~integrins~~ the alpha 5 and beta 1 subunits, which together make up the fibronectin receptor in their naturally paired state, in MCF-7 and T-47D cells but had no effect on constitutively very high levels of ~~integrin~~ the alpha 5 subunit in MDA-MB-231 cells. The block in growth of FGF-2-treated cells on fibronectin was further accentuated by pre-treatment of the cells with an anti-~~integrin~~ alpha 5 subunit antibody, strongly suggesting a role for fibronectin in supporting the survival of dormant breast cancer cells in bone marrow. Blocking peptides that disrupt the interaction of fibronectin with ~~their~~ its integrin receptor that

downregulated the expression of the alpha 5 beta 1 integrins ~~alpha 5 and beta 1~~ also reversed the survival effects of fibronectin binding to cells in the presence of FGF-2. FGF-2 also induced the phosphorylation of the kinase Akt involved in survival signaling. All *trans* retinoic acid was able to reverse Akt phosphorylation induced by EGF and reversed FGF-2 induced increases in total and Phosphorylated Akt, suggesting an additional mechanisms of disrupting survival in these cells.

[0125] Example 6. Disruption of the PI3K/Akt signal pathway may disrupt support for breast cancer colony growth by fibronectin

FGF-2-induced phosphorylation of Akt may be disrupted in a number of ways by disrupting the interaction of fibronectin with integrin α5β1 by downregulating the expression of the ~~integrins~~ α5 and β1 subunits, with other transcription factor inhibitors, retinoids, antisense oligonucleotides, disruption of their interaction with blocking antibodies to the integrins ~~α5,~~ β1 or fibronectin, or kinase inhibitors that inhibit activation of PI3K or Akt. Examples of Akt inhibition are shown in Figure 11, where incubation of MCF-7 cells with ATRA reversed the EGF-mediated phosphorylation of Akt, as demonstrated on a Western blot, and Figures 15 and 16 where inhibition of Akt and PI3K, the upstream activation of Akt inhibits survival of dormant clones. This approach may also provide an array of mechanisms for disruptive survival signaling through the PI3K pathway to breast cancer cells at metastatic sites initiated by interaction of integrin α5β1 with fibronectin. Disruption of signaling pathways, kinases and GTPases may disrupt signaling initiated by interaction of fibronectin with the integrins alpha 5 ~~and~~ beta 1 in cancer cells that can support survival in these cells. Examples are included which were conducted with inhibitors of Rhp, Rho kinase and MEP/MAp kinase, p38, PKC and PKA resulting in the survival of dormant clones on fibronection (Figures 17A and B).